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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,790	03/26/2004	Maurice Zauderer	1843.0120001/AJK	7155

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STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/809,790	ZAUDERER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *20-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 10/3/05 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-19), and species of cell surface markers from tumor cells and species of antigenic peptide derived from an infectious agent/infected cell in response filed 3/14/05.

Claims 1-19 and 61 are presently being examined.

The following are new grounds of rejection.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 12-14, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed composition comprising one or more MHC class I α3 domains comprising β2m and an antigenic peptide, and an antibody or fragment thereof which binds a T cell surface marker, including a co-stimulatory molecule recited in the instant claims, or which binds a cell surface marker of an infected cell, or an antigenic peptide from an from infected cell or from a target tissue from an autoimmune disease.

The instant claims encompass a composition that comprises fragments of an isolated MHC class I alpha 3 domain and a fragment of a β2m molecule that associates with an MHC class I alpha 3 domain and an antibody or fragment of an antibody specific for a cell surface marker, including those recited in the instant claims, wherein the cell surface marker recognized by the antibody or fragment thereof is a T cell surface marker, including a co-stimulatory molecule selected from the group consisting of CD28, CTLA-4 and CD25, or said cell surface marker is of an infected cell, or wherein the antigenic peptide is derived from the target tissue of an autoimmune disease.

The instant specification discloses that an MHC class I alpha 3 domain fragment is identical to the sequence described by Fayen *et al* (1995), and that fragment that has substitutions of less than 1-20 amino acids which result in no more than a factor of 10 reduction in affinity for β2m or extends further into the transmembrane and/or the alpha 2 domain of the native alpha chain sequence and to which β2m binds with an affinity that remains less than one tenth the binding affinity of β2m for the intact MHC class I alpha chain or is shorter by any amount which is still compatible with no more than a factor of 10 reduction in affinity for β2m will be referred to as an MHC class I alpha 3 domain ([0017], [0040]). The specification further disclose that fragments of β2m that are useful in the invention would have to retain the ability to associate with the MHC class I alpha 3 domain, and preferably, retain the ability to associate with other domains of the intact alpha chain ([0042]). The specification discloses that the antibodies of the invention target the alpha 3 domain/β2m /peptide complexes to target cells ([0011], [0012]). The specification discloses antigen binding antibody fragments that are Fab, $F(ab')_2$, Fv and scFv ([0064], [0067]). The specification further discloses that peptides derived from agents for infectious disease include HIV-1 MNr gp 160 peptide and HTLV-1 Tax 11-19 peptide (Table 3 on page 21).

The specification discloses that the antigenic peptide may be derived from a target tissue from an autoimmune disease, but does not provide disclosure of species of such antigenic peptides, nor of working examples of complexes of the instant invention that comprise such peptides ([0060]. The specification discloses species of antigenic peptides that bind to HLA class I molecules, but does not disclose species of cell surface markers of infected cells, nor working examples of antibodies to cell surface markers of infected cells ([[0058], [0068]). The specification discloses species of human leukocyte differentiation antigens or cell surface markers, but does not disclose complexes of the instant invention that comprise antibodies or fragments thereof with specificities for these antigens ([0097]), *i.e.,* if the antibody specificity was directed towards a T cell surface marker, the complex of antibody-alpha3-β2m-peptide would be attached to the T cell, and unless the T cell was in the vicinity of a target cell, β2m-peptide exchange into the class I MHC complex of the target cell would not occur. In addition, the specification discloses that some human CTLA-4 specific antibodies inhibit the responses of resting human CD4+ T cells and that the mechanisms of inhibition for CTLA-4 specific mAbs have not been fully characterized and may be mediated by either or both a direct inhibitory effect on T cells that have up-regulated expression of CTLA-4 or through activation of a subset of inhibitory T cells that express high levels of CTLA-4 ([0090]). The specification discloses that anti-CD25 fusion proteins could specifically target activated T cells ([0089]), however, such fusion proteins could also target T regulatory cells that are $CD25^+$. The specification does not disclose working examples wherein peptides from infectious agents such as HIV may be used.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera of complexes comprising antigenic peptides from autoimmune tissues, and/or antibodies or fragments thereof specific for cell surface markers from infected cells or specific for T cell surface markers, including co-stimulatory molecules. In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein.

5. Claims 1-19 and 61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to Fayen *et al* (Mol. Immunol. 32(4): 267-275, 1995) in the specification at [0017] is improper because essential matter can only be incorporated by reference to (1) a U.S. patent or (2) a pending U.S. application, subject to the conditions set forth below.

Essential material is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates essential material by reference, or (4) a foreign application.

Essential material may not be incorporated by reference to non-patent publications, and the specification at [0017] refers to the fragment of complete human HLA-A*0201 alpha chain sequence taught by Fayen *et al* and disclosed substitutions thereto "will be referred to as an MHC class I α3 domain."

Although Applicant has amended the specification in the amendment filed 10/8/02 to clarify that the sequence taught by Fayen *et al* is the same as SEQ ID NO: 1, the amendment must be accompanied by an affidavit or declaration executed by the Applicant, or a practitioner representing the Applicant, stating that the amendatory

material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

6. Claims 12-14, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, a composition comprising one or more MHC class I alpha 3 domain or fragment thereof, and β2m or fragment thereof, and antibody or fragment thereof.

The specification has not enabled the breadth of the claimed invention because the claims encompass a composition that comprises an isolated MHC class I alpha 3 domain fragment thereof of, an β2m or fragment of a β2m molecule that associates with an MHC class I alpha 3 domain and an antibody or fragment of an antibody specific for a cell surface marker, including those recited in the instant claims, wherein the cell surface marker recognized by the antibody or fragment thereof is a T cell surface marker, including a co-stimulatory molecule selected from the group consisting of CD28, CTLA-4 and CD25, or said cell surface marker is of an infected cell, or wherein the antigenic peptide is derived from the target tissue of an autoimmune disease, or wherein the antigenic peptide is from an infectious agent or from infected cells.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used.

The instant specification discloses that an MHC class I alpha 3 domain fragment is identical to the sequence described by Fayen *et al* (1995), and that fragment that has substitutions of less than 1-20 amino acids which result in no more than a factor of 10 reduction in affinity for β2m or extends further into the transmembrane and/or the alpha 2 domain of the native alpha chain sequence and to which β2m binds with an affinity that remains less than one tenth the binding affinity of β2m for the intact MHC class I alpha chain or is shorter by any amount which is still compatible with no more than a factor of 10 reduction in affinity for β2m will be referred to as an MHC class I alpha 3 domain ([0017], [0040]). The specification further disclose that fragments of β2m that are useful in the invention would have to retain the ability to associate with the MHC class I alpha 3 domain, and preferably, retain the ability to associate with other domains of the intact alpha chain ([0042]). The specification discloses that the antibodies of the invention target the alpha 3 domain/β2m /peptide complexes to target cells ([0011], [0012]). The specification discloses antigen binding antibody fragments that are Fab, $F(ab')_2$, Fv and scFv ([0064], [0067]).

The specification discloses that the antigenic peptide may be derived from a target tissue from an autoimmune disease, but does not provide disclosure of species of such antigenic peptides, nor of working examples of complexes of the instant invention that comprise such peptides ([0060]. The specification discloses species of antigenic peptides that bind to HLA class I molecules, but does not disclose species of cell surface markers of infected cells, nor working examples of antibodies to cell surface markers of infected cells ([[0058], [0068]). The specification discloses species of human leukocyte differentiation antigens or cell surface markers, but does not disclose complexes of the instant invention that comprise antibodies or fragments thereof with specificities for these antigens ([0097]), *i.e.,* if the antibody specificity was directed towards a T cell surface marker, the complex of antibody-alpha3-β2m-peptide would be attached to the T cell, and unless the T cell was in the vicinity of a target cell, β2m-peptide exchange into the class I MHC complex of the target cell would not occur. In addition, the specification discloses that some human CTLA-4 specific antibodies inhibit the responses of resting human $CD4^+$ T cells and that the mechanisms of inhibition for CTLA-4 specific mAbs have not been fully characterized and may be mediated by either or both a direct inhibitory effect on T cells that have up-regulated expression of CTLA-4 or through activation of a subset of inhibitory T cells that express high levels of CTLA-4 ([0090]). The specification discloses that anti-CD25 fusion proteins could specifically target activated T cells ([0089]), however, such fusion proteins could also target T regulatory cells that are $CD25^+$, as is evidenced by Hoffmann *et al.*

Evidentiary reference Hoffman *et al* (Blood 104(3): 895-903, 8/2004) teach that $CD4^+CD25^+$ regulatory T cells are pivotal for the maintenance of self-tolerance, and that their adoptive transfer gives protection from autoimmune diseases and pathogenic alloresponses after solid organ or bone marrow transplantation in murine model systems (especially abstract).

The specification further discloses that peptides derived from agents for infectious disease include HIV-1 MNr gp 160 peptide and HTLV-1 Tax 11-19 peptide (Table 3 on page 21).

Evidentiary reference Ogg *et al* (British J. Cancer 82(5): 1058-1062, 2000) teach that using an HLA class I complex containing a peptide from the HIV gag protein would not be ideal for *in vivo* application, but that rather, for clinical work, MHC class I molecules refolded with peptides from EBV may be a more effective choice, as anti-EBV CTL response persists at significant levels for years after primary infection and may be repeatedly re-activated during life, providing natural boosts in the frequency and activation of CTL which might be re-targeted at tumors (especially first full paragraph at column 2 on page 1061).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
November 25, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600